

This Week's Citation Classic

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Albert A, Goldacre R & Phillips J. The strength of heterocyclic bases.

J. Chem. Soc. 1948:2240-9.

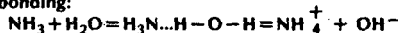
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Noting that the determination (and interpretation) of ionization constants of heterocyclic bases was a largely unexplored territory, this paper reported and discussed values for 120 examples from 30 unsaturated ring-systems. The large increment in basic strength, found when an amino group was placed α - or γ - to a ring-nitrogen atom, was explained by an additional resonance that valence permitted in the cation alone. [The *SCI*[®] indicates that this paper has been cited in over 295 publications since 1961.]

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"Curiously enough, determination of the ionization constants of organic bases lagged far behind that of acids. This late start followed from a theoretical uncertainty as to how ammonia became ionized. In 1912, Moore and Winmill¹ showed that nitrogenous bases do not directly withdraw a proton from water to give the cation, but form an unstable hydrate by what we now know as hydrogen bonding:



"Because the relative rates of these two equilibria were unknown, doubt remained in assigning any observed constant. However, by 1930, rapid measuring techniques had shown both reactions to be virtually instantaneous, and hence the experimental results slowly became accepted as true ionization constants. Accordingly, Hall and Sprinkle, in Wisconsin, determined ionization constants for 60 aliphatic and aromatic bases such as methylamine and aniline.² They used potentiometry with a hydrogen electrode. This work was not extended to the heterocyclic bases which tended to be reduced by the hydrogen electrode and also to poi-

son it. The only alternative, conductimetry, was not seriously entertained because of the large CO_2 error.

"The discovery of the glass electrode³ followed by the marketing of it in potentiometer assemblies ('pH sets') opened up new possibilities. In 1941, Reginald Goldacre (at that time a graduate student) and I started to tackle this problem, beginning with the aminoacridines for which we demonstrated the close parallel that exists between ionization (at pH 7) and antibacterial action.⁴ This work attracted attention from the Australian Army because aminoacridine irrigations were their standard treatment of deep, highly infected wounds in World War II. From that point, we never lacked funds to pursue the acridine work,^{5,6} in the course of which we co-opted John Phillips and broadened our field to include all the principal heterocyclic bases.

"The cited paper was well received because it provided, for the first time, a set of self-consistent data (with interpretations) for all the common heteroaromatic bases. Existing misconceptions were set right; e.g., many workers had thought that inserting a second nitrogen atom into the pyridine ring would strengthen it whereas this operation proved to be highly base-weakening. We explained why this was so, and showed that the phenomenon is quite general. Moreover, we demonstrated the weakness of several bases (e.g., cinno-line) that had been classed as 'strong' because a specimen had turned litmus paper blue thanks to residual alkali used in liberating the base!

"Perhaps the most surprising, and widely applicable, result was the great strengthening found when an amino group was inserted in positions α - or γ - to a ring-nitrogen atom. We showed that the resulting structures were parallel to those of amidines and vinylogous amidines (respectively), and we traced the large increment in basic strength to the extra resonance provided by the cation alone.

"By 1948, when we published the cited paper, we three investigators had left the University of Sydney, where the work was done. Each of us had developed research interests of his own, but we have always remained in touch. The cited work triggered many other determinations of heterocyclic base constants, the results of which I collect regularly."^{7,B}

1. Moore T S & Winmill T F. The state of amines in aqueous solution. *J. Chem. Soc.* 101:1635-76, 1912.
2. Hall N F & Sprinkle M R. Relations between the structure and strength of certain organic bases in aqueous solution. *J. Amer. Chem. Soc.* 54:3469-85, 1932. (Cited 185 times.)
3. Dole M. *The glass electrode*. New York: Wiley, 1941. 332 p.
4. Albert A, Rubbo S D & Goldacre R. Correlation of basicity and antiseptic action in an acridine series. *Nature* 143:332-3, 1941.
5. Albert A & Goldacre R. The nature of the amino-group in aminoacridines. *J. Chem. Soc.* 1943:454-62.
6. -----, The ionization of acridine bases. *J. Chem. Soc.* 1946:706-13.
7. Albert A. Ionization constants. (Katritzky A R, ed.) *Physical methods in heterocyclic chemistry*. New York: Academic Press, 1963. Vol. 1. p. 1-108.
8. -----, Ionization constants. (Katritzky A R, ed.) *Physical methods in heterocyclic chemistry*. New York: Academic Press, 1971. Vol. 3. p. 1-26.